Date: February 27, 2002

To: BLA STN 103780 file

From: Gibbes Johnson

Through: Amy Rosenberg, M.D., Barry Cherney, Ph.D.

Re: **Part I**. Review of Amendment dated May 16, 2001 describing CMC changes in the manufacture of Rebif (interferon β1a). **Part II**. Review of Sponsor's response to the Agency's CMC Discipline Review Letter dated January 29, 2002.

Part I. Review of Amendment dated May 16, 2001 describing CMC changes in the manufacture of Rebif.

The following is an itemized list of changes which have been made in the manufacturing of Rebif with additional information on each change as appropriate:

Drug Substance Changes

1. The existing production facility has been expanded and modified. These changes have been reviewed by Daniel Kearns in DMPQ/OC and were considered relatively minor.

2. XXXXXXXXXX

3. XXXXXXXXXX

4. In addition to the current source of XXXXXXXXXX, Serono has qualified XXXXXXXXXX as an additional source of XXXXXXXXXX. This alternative source have been qualified and shown to be equivalent to the XXXXXXXXXX in terms of cell culture performance in the XXXXXXXXXX and the quality of interferon bulk produced. Representative XXXXXXXXXX for these lots were presented in Appendix 2.

5. Based on experience gained with the cell culture process, the in-process cell culture control parameter for the amount of IFN beta-1a/mL in harvest will be modified from

XXXXXXXXXXX as described in section 2.2.2.4. As described in 21 CFR 211.186 (Master production and control records) "a statement of yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 21 CFR 211.192 is required". Thus, this change is not acceptable.

6. A XXXXXXXXXX of the current purification process (described in the original BLA file) is being proposed as an alternate scale purification process for interferon beta-la. The XXXXXXXXXX. Full details of the purification process and details of the validation are provided for in section 2.2.4. XXXXXXXXXX confirming that the quality of the product is not affected. All critical in-process acceptance criteria and release specifications were met. The following 3 sections summarize the data presented in the amendment regarding this XXXXXXXXXX:

A. Proof of Structure Determination
XXXXXXXXXX

B. Validation of the 4X Process
XXXXXXXXXX

C. 4X Drug Substance Stability
XXXXXXXXX

7. XXXXXXXXXX

8. Serono has developed an improved shipping package with better sealing properties to be used for shipment of XXXXXXXXXX bulk purified IFN beta-la to XXXXXXXXXX. The improved package and shipping validation data XXXXXXXXXX and at accelerated temperatures XXXXXXXXXX are described in section 2.2.6

9. The policy which describes Serono's preparation and acceptance of new production reference standards (PRB) has changed. New and improved analytical test methods

have been developed to characterize and accept new reference standards. A full description of the new methods is provided in section 2.2.7. XXXXXXXXXX.

10. Modifications have been made to the specifications and test methods used to accept/reject individual lots of bulk purified IFN beta-1a. Serono is changing two current test methods, and removing three specifications. Complete descriptions of the proposed changes are provided in section 2.2.8. Validation data and information supporting these changes is provided for in section 2.2.8.2.

a. XXXXXXXXXX.
b. XXXXXXXXXX.
c. XXXXXXXXXX.
d. XXXXXXXXXX.
e. XXXXXXXXXX.

11. XXXXXXXXXX.

Drug Product Changes:

12. XXXXXXXXXX. These modifications are described in section 2.3.1. These changes have been reviewed by Daniel Kearns in DMPQ/OC and considered relatively minor.

13. Two additional FDA licensed suppliers of Albumin (human) are being added to this application (XXXXXXXXXX). The additional suppliers of Albumin (human) are XXXXXXXXXX, as described in section 2.3.2.

14. Serono has modified the packaging of Rebif pre-filled syringes to include a rigid needle shield protector to minimize inadvertent damage to the needle. A more complete description of the packaging is provided in section 2.3.3.

Summary of Part I

The manufacturing changes described in this amendment are all acceptable with the exception of items # 5 and #11. A CMC Discipline Review letter was issued on January 29, 2001 to address these concerns and additional issues. See Part II below regarding the CMC Discipline Review letter.

Part II. Review of Sponsor's response to the Agency's CMC Discipline Review Letter dated January 29, 2002. The sponsor's response is dated February 5, 2002 and DARP Log #76782, document barcode 1111878

The agency's comment from the Discipline Review letter is provided first followed by the sponsor's response.

DR #1. According to 21 CFR 211.186, the master production and control records require "a statement of yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 21 CFR 211.192 is required". Thus, the in-process cell culture control parameter for the amount of Interferon beta-la/mL in harvest cannot be XXXXXXXXXX.

Sponsor's response: Serono committed to retain this in-process range specification as described in the original BLA.

Assessment of Sponsor's response: Response is acceptable.

DR #2. Please submit to the BLA, stability data on Interferon beta-1a drug product produced with the drug substance manufactured using the XXXXXXXXXX process.

Sponsor's response: Drug product has an established expiration date of 24 months when

stored at 2-8 C. Serono provided real time (2-8 C) and accelerated (XXXXXXXXXX) stability data for XXXXXXXXXX batchs of 22 ug Rebif and XXXXXXXXXX batch of Rebif 44 ug (all derived from XXXXXXXXXX drug substance). The 22 ug batchs XXXXXXXXXX arose from drug substance batchs XXXXXXXXXX, respectively. The 44 ug batch XXXXXXXXXX was generated using XXXXXXXXXX. Real time XXXXXXXXXX stability data were provided for batch XXXXXXXXXX and XXXXXXXXXX real time data were provided for XXXXXXXXXX. Real time XXXXXXXXXX stability data were provided for batch XXXXXXXXXX. Accelerated stability data (XXXXXXXXXX) were provided for all XXXXXXXXXX batchs out to XXXXXXXXXX. Real time and accelerated data included the following assays: appearance of solution, clarity/opalescence, color of solution, pH, osmolarity, XXXXXXXXXX, protein content, XXXXXXXXXX, sterility and bacterial endotoxins. In all instances, all parameters tested remained within specifications and no trends were observed indicating that stability profiles of drug products produced from XXXXXXXXXX drug substance are comparable. The real time stability studies at 2-8 C are ongoing.

Assessment of Sponsor's response: Review of the data supports the 24 month expiration dating for drug product manufactured using XXXXXXXXXX drug substance. Response is acceptable.

DR #3. With regard to the extension of the drug substance retest date to XXXXXXXXXX, please note that for biological substances it is more appropriate to establish a shelf life than a retest period. While we concur that the product remains stable for up to XXXXXXXXXX, release of drug substance stored for periods greater than XXXXXXXXXX should be based on data derived from a prescribed stability protocol, rather then from retesting that confirms continued compliance to specifications. Therefore, upon approval, we intend to designate a shelf life for the bulk drug substance and not a retest period.

Sponsor's response: Serono concurs that a shelf life, rather than a retest period is appropriate and release of drug substance will be based upon data derived from a prescribed stability protocol.

Assessment of Sponsor's response: Response is acceptable.

DR #4. The agency strongly recommends Serono consider using a XXXXXXXXXX as a source for XXXXXXXXXX-derived materials used in the manufacture of Interferon beta-1a.

Sponsor's response: Serono committed to consider this and will consult with its suppliers to determine the feasibility of the recommendation. XXXXXXXXXX serum is the only XXXXXXXXXX-derived material used in manufacture.

Assessment of Sponsor's response: Response is acceptable.

Summary of Part I and Part II

The manufacturing changes described in the amendment are all acceptable and the responses to the CMC Discipline Review letter are all acceptable.